DISEASE MODIFICATION STRATEGIES FOR AD

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Atopic dermatitis: pruritus constant but frequently omitted

Pruritic inflammation: hallmark of AD

Another frequently omitted point: Atopic dermatitis, a disease of the adult,...and of the elderly!
Medicine: Evolution, not Revolution

Anatomo-clinical Medicine

Pastorian (etiological) Medicine

Evidence-Based Medicine

Relation to translational medicine

Individualized (molecular) Medicine

Circa 1800

Circa 1870

Circa 1980

Circa 2010
Translational medicine needed to implement personalized medicine

- **Translational medicine** is a discipline within biomedical and public health research that aims to improve the health of individuals and the community by “translating” findings into diagnostic tools, medicines, procedures, policies and education *(Wikipedia)*

- **Main objective**: new cures for disease can be delivered faster to patients

- **How it works**: multi-disciplinary, highly collaborative, “bench-to-bedside” approach.
Topical treatments: from topical hydrocortisone (1950s) to topical calcineurin inhibitors (1997)

Wise F, Sulzberger MB. 1933 Year Book of Dermatology and Syphilology; 38-39.

Definition of AD

Sulzberger MB., Witten VH

First data on topical steroids

Marion Baldur Sulzberger
1895-1983
From Sulzberger’s introduction of TCS, more than 50 years to validate an active antiinflammatory maintenance treatment in AD

What is already known on this subject
Atopic dermatitis is characterised by frequent, unpredictable relapses, and there is little evidence to support any of the commonly used practices for long term maintenance treatment of moderate to severe cases

What this study adds
After stabilisation of an acute flare, adding fluticasone propionate cream or ointment twice weekly to daily emollient treatment significantly reduced the risk of patients experiencing a further relapse and extended remission time

This regimen seemed to be well tolerated, with a low risk of local adverse effects, and may paradoxically be steroid sparing since, by producing longer remission periods, it should reduce the need for intensive treatment with topical corticosteroids as is often required to control flares

We expect to see more efficient clinical trials based on a more thorough understanding of the genetic basis of disease. We also anticipate that some previously failed medications will be recognized as safe and effective and will be approved for subgroups of patients with specific genetic markers.
Can I fish something here?

This is not evidence-based!

ISAD Arcachon, 2005
How to adapt Evidence-Based Medicine?

Strategy: begin with homogeneous populations
Importance for AD therapy? One or several AD?

« ECZEMA »

« nébuleuse » (Nebula) des névrodermites (neurodermatitis), 1896

Louis Brocq 1856-1928
Is the paradigm Atopic /Non atopic AD important for designing interventions?

Johansson et al, JACI 2004

Eczema

Atopic eczema  Non atopic eczema

IgE

2 endophenotypes??

Eyerich & Novak, 2013

4 endophenotypes??

Genetic immunology type (TSLP, IL-4/IL-13, TLR-2, IgE/FceRI)

Genetic barrier type (filagrin, Spink/LEKTI, hornerin)

Non-genetic immunology type (allergic sensitization)

Non-genetic barrier type (dryness, scratching, microbial, toxic, phototoxic)
Better translation: the perception from Pharma (e.g. Novartis)

From rare to common disorders: a paradigm shift in Pharma to improve the ratio NME-POC

New Molecular Entity Portfolio

Successful Proof-of-Concept Trials

1:10
Translational concept: from rare to common

ACZ885: anti IL-1β for inflammation

Investigational. Efficacy and safety have not been established.

Source for patient numbers: global prevalence estimate from Patient Base.
Application of this strategy to AD

**Allergies**

Skin permeability

- Netherton syndrome is a genetic disorder. It is manifested by a severe impairment of the skin barrier function, with severe atopic dermatitis.

Over-active Protease

[Diagram showing skin barrier before and after treatment with BPR277]

- Defective skin barrier
- Restored skin barrier
- Allergen and pathogen penetration, dehydration, infection
2014: current drug/device development for AD

- **315 studies found for:** atopic dermatitis | Exclude Unknown | Interventional Studies
- **58 studies found for:** atopic dermatitis | Open Studies | Exclude Unknown | Interventional Studies
- **22 studies found for:** atopic dermatitis | Completed | Exclude Unknown | Studies With Results | Interventional Studies
- **196 studies found for:** atopic dermatitis | Completed | Exclude Unknown | Studies Without Results | Interventional Studies

Clinicaltrials.gov, May 2014
In development

• **Barrier restoring devices** (emollients, antiproteases, urocanic acid, bacterial transplants…)

• **Itch controllers**
  – S-777469 cannabinoid receptor 2 selective agonist SHIONOGI INC.
  – VLY-686 neurokinin-1 receptor antagonist VANDA PHARMA
  – DNK 333 dual tachykinin NK1/NK2 receptor antagonist antagonist NOVARTIS
  – SB705498: TRPV1 antagonist, GSK
  – CT 327 TrkA kinase inhibitor (neurogenesis), CREABILIS SA

• **Oral/topical antiinflammatory drugs**
  – SEGRAs derived from corticosteroids, BAYER
  – Anti PDE4, GSK, EISAI, OTSUKA,DERMIRA, PRECISION DERM, ANACOR
  – CRTH2 (DP1, 2) antagonists, NOVARTIS, ATOPIX, TAISHO
  – Janus kinase inhibitors (tofacitinib) PFIZER ...

Clinicaltrials.gov, May 2014
AD Clinical Trials registered biologics

- Dupilumab anti receptor IL4/13 Regeneron
- QGE031 Anti IgE Novartis
- MEDI4212 Anti IgE MedImmune
- Ustekinumab JANSSEN
- ILV-094 anti IL-22 Antibody
- AMG 157 anti TSLP receptor AMGEN
- Anti-Interleukin 31 Bristol-Myers Squibb
- CIM331 CHUGAI Anti-IL-31 receptor humanized monoclonal
- FURESTEM-AD mesenchymal stem cells KANG STEM BIOTECH CO., LTD. Korea
Importance of the medical perspective: several phases, several strategies

**Initiation phase**
- No symptom /dry skin
- **Epidermal barrier impaired (FLG)**
- Skin innate immunity (TLR, peptides)
- Epigenetics
- Skin microflora
- Others:pH, temperature…
- Stress
- Dendr cells/Macroph

**Revelation phase**
- Pruritus+++ «contact » AD
- Reversible
- **Antigens**
- Tolerance yes/no
- Eosinophils, T cells
- Id +
- Tregs-TH2
- TSLP,IL31…

**Chronic phase**
- Pruritus+++ Flexural stable AD
- **Cutaneous immune system**
- Autoinflammation
- Unmasking autoAg
- T cells, Macrophages
- Tregs?
- TH17?
- TH22?
- TH1?
- CD23?

**Extracutaneous phase**
- Asthma/rhinitis
- Resp epithelial barrier
- Innate immunity (resp)
- Basophils, eosinophils, T cells, Macroph, Mast cells
- Link with skin ? TSLP

**Key factors**
- Immunosuppressive drugs
- Targeted biologics (TSLP, IL31, IL22, ustekinumab…)
- Local antiinflammatory drugs
- antihistamines
- Immunotherapy(resp)

**Strategies**
- Primary prevention
- Barriers, microflora
- Local Antiinflammatory drugs
- Immunotherapies (skin)
- Prevention extracutaneous involvement
- **Imbrication addition…, link with other barriers (digestive, respiratory)**

**Situating interventions according to phases +++**

(Taieb et al, JDDG, 2011)
Initiation phase: before drug intervention, some basic issues not solved, e.g. bathing

- Vienna school (Hebra, Kaposi):
  - major importance of local treatments and water use, bathing, showers

- Besnier (1897):
  - "Baths of any kind should be given to children with eczema sparingly, based on specific indications"

- Marfan (1928):
  - "Do not bathe the infant with eczema (...) You just wash integuments with warm boiled water or better with an emollient water as bran in water, then dried thoroughly with sterilized cotton wool."

- Babonneix (1935):
  - « Just omit bathing »
Common to all clinical phases: need to fight itch

- "Let's remember that the clinical benefit of the patient must prevail ... trying to find an effective way to combat the itch of eczema. This point should be considered at the next Congress”

Excerpted of the proceedings of Paris 1900 WCD about the theory of Unna

Current perspective: can itch be understood From the perspective of « allergic » inflammation?

Paul Gerson Unna 1850-1929 and the microbial theory of eczema
« Neurodermatitis » from Jacquet’s experiment to current intervention strategies


Histoire de la Dermatite Atopique, 2004
# Pruritus, nerves, inflammation

## 1. Peripheral mediators

<table>
<thead>
<tr>
<th>Source</th>
<th>Mediators</th>
<th>Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mast cells</td>
<td>Histamine</td>
<td>H1 (H4?)</td>
</tr>
<tr>
<td>Nerves</td>
<td>Substance P</td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Reactive oxygen</td>
<td></td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>Artemin</td>
<td></td>
</tr>
<tr>
<td>Keratinocytes</td>
<td>Nerve growth factor, semaphorin 3A</td>
<td></td>
</tr>
<tr>
<td>T cells</td>
<td>IL-2</td>
<td>IL-2 receptor</td>
</tr>
<tr>
<td></td>
<td>IL-31</td>
<td>IL-31 receptor</td>
</tr>
<tr>
<td>Endothelial cells</td>
<td>Endothelin</td>
<td>ACh receptor</td>
</tr>
<tr>
<td></td>
<td>Acetylcholine</td>
<td></td>
</tr>
</tbody>
</table>

## 2. Central mediators

<table>
<thead>
<tr>
<th>Mediators</th>
<th>Receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encephalin</td>
<td>μ receptor (pruritogenic)</td>
</tr>
<tr>
<td>Morphine/opioid</td>
<td>κ receptor (anti-pruritogenic)</td>
</tr>
</tbody>
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Kabashima, 2013

Tominaga & Takamori, 2014

TSLP, a newcomer

Wilson et al, 2013
Intervention on epidermal nerve sprouting?

Itch and nerve fibers with special reference to atopic dermatitis: Therapeutic implications

Mitsutoshi TOMINAGA,¹ Kenji TAKAMORI¹,²

J Dermatol 2014
Link to «allergic» cytokines? Monogenic dermatological model: lichen amyloidosis and IL31-OSM
IL-31 and IL-31R in AD skin

Kato et al, JDS, 2014
The Epithelial Cell-Derived Atopic Dermatitis Cytokine TSLP Activates Neurons to Induce Itch

Sarah R. Wilson,1,2,3 Lydia Thé,1,3 Lyn M. Batia,1 Katherine Beattie,1 George E. Katibah,1 Shannan P. McClain,1 Maurizio Pellegrino,1 Daniel M. Estandian,1 and Diana M. Bautista1,2,*

Cell, 2013
Calcipotriol-induced mouse AD and TSLP

Effect abolished in TSLP-/- mouse

Zhang et al, PNAS 2009

Adjunctive effect of epidermal TSLP on distant airways allergic sensitization
What can be translated from non-allergic inflammation?

- T cell–mediated allergic disease probably involves multiple chemokines and their receptors, the relative roles of which will vary depending
  - on the affected organ
  - on the temporal phase of the disease.
- Test of existing drugs used in non-allergic inflammatory diseases recommended in recalcitrant AD as POC
Biologics and targeted therapies: significant failures and ongoing development in AD

- Anti-IgE (competes with IgE high affinity receptor): **omalizumab** others in development (Novartis, Medimmune)
  - Pathogenic role of IgE unclear in AD
- Anti T Cell recruitment/trafficking/activation: **efalizumab**, **alefacept**, **anti PD2 receptors**
- Anti B cell: **rituximab** (anti CD 20)*
- Anti TNF: **infliximab**
- Anti IL4-IL13 (TH2 cytokines) and receptor: **nuvance**, **pitrakinra**, **dupilumab**, **librikizumab**
- Anti IL5 (eosinophils): **mepolizumab**, (anti PD2 receptors)

*Simon et al, JACI 2008, 6 patients treated
How to translate faster crucial lab data on pruritogenic inflammation into practice?

Increased Epidermal Cell Proliferation in Normal Human Skin \textit{in Vivo} Following Local Administration of Interferon-\textgamma

Jonathan N. W. N. Barker,* John R. Goodlad,†
Elizabeth L. Ross,* Carmen C. Yu,‡
Richard W. Groves,* and
Donald M. MacDonald* 1993

Studies of Human C5a as a Mediator of Inflammation in Normal Human Skin

Kim B. Yancey, Carl H. Hammer, Liana Harvath, Lois Renfer, Michael M. Frank, and Thomas J. Lawley 1984
Summary and conclusions

- Therapy according to stage of natural history of AD in addition to severity.
- Therapy according to genetic subtype???
- Prevention: public health dimension of the problem for food allergy and asthma +++
- (Too?) many druggable targets, many existing products not yet tested to fight pruritic inflammation: justification of ongoing and future POC pilot trials (e.g.: anti IL6, anakinra IL1R)
- Need of faster POC studies